Exhibit C

Improved Survival with Plasma Exchange in Patients with Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome

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PURPOSE: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are uncommon disorders that are generally fatal if left untreated. Plasma exchange therapy is associated with high response rates and improved short-term survival, but most previous studies have been limited by small numbers of patients or short duration of follow-up.

METHODS: We performed a retrospective cohort analysis in 126 consecutive patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, most of whom were treated principally with plasma exchange at the Sacramento Medical Foundation Blood Center and the University of California Davis Medical Center between 1978 and 1998. We measured the effect of therapeutic plasma exchange on 30-day mortality, response rate, and overall survival, and determined which factors were associated with 30-day mortality and relapse.

RESULTS: The overall 30-day mortality was 10% of the 122 patients who received plasma exchange as their principal treatment (a median of 9 exchanges and a mean cumulative infused volume of 43 ± 77 L fresh frozen plasma); 56% were complete responders and 21% were partial responders. The relapse rate was 13%. The estimated 2-year survival was about 60%; among patients without serious underlying comorbid conditions, the estimated 2-year survival was about 80%. Each unit increase in clinical severity score (on a 0 to 8 scale) was associated with a 2.2-fold (95% confidence interval [CI]: 1.3 to 3.9) increase in the odds of 30-day mortality. Patients who were febrile at presentation were substantially less likely to suffer a relapse (odds ratio = 0.2; 95% CI: 0.03 to 0.9).

CONCLUSION: Plasma exchange therapy produced high response and survival rates in this large cohort of patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. The Clinical Severity Score may be useful in predicting 30-day mortality, whereas fever at onset was associated with a lesser risk of relapse. Prospective studies should stratify patients according to these prognostic factors. **Am J Med. 1999;107: 573–579.** ©1999 by Excerpta Medica, Inc.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome are rare, closely related disorders of unclear etiology that are characterized by microangiopathic hemolytic anemia and thrombocytopenia. TTP, the more severe form, was first reported by Moschowitz (1) in 1925. It is classically described as a clinical pentad of hemolytic anemia, thrombocytopenia, neurologic symptoms, renal involvement, and fever (2), although only a minority of patients present with all 5 characteristics (3). Hemolytic uremic syndrome, first described by Gasser et al (4) in 1955, may present with profound thrombocytopenia but its clinical picture is dominated by renal insufficiency.

There have been several insights into the pathogenesis of TTP. First, unusually large multimers of von Willebrand factor were recognized in patients' plasma (5). Later, it was demonstrated that lack or inhibition of von Willebrand factor-cleaving protease may account for this observation (6,7). An infectious cause has also been implicated in the pathogenesis of TTP: Tarantolo and colleagues (8,9) reported the presence of intra-erythrocytic *Bartonella*-like organisms in patients with TTP, and treatment with doxycycline has resulted in the amelioration of symptoms in some patients.

Without treatment, TTP is a virulent, progressive disease, with a mortality rate in excess of 95% (10). In several case series, plasma exchange has been shown to produce response rates of about 80% and survival rates greater than 90% (11). The efficacy of plasma exchange compared with plasma infusion was confirmed in a randomized trial (12). As TTP and hemolytic uremic syndrome are presumed to have a similar underlying pathogenesis, therapy has been similar for both disorders (13). Because these syndromes are fulminant and often fatal, treatment is usually initiated as soon as the diagnosis of microangiopathic anemia and thrombocytopenia is made.

We report our 20-year experience involving 126 patients with TTP or hemolytic uremic syndrome, most of whom were treated principally with plasma exchange. We evaluated their response to treatment, mortality in the first 30 days following the diagnosis, relapse rate, and

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Table 1. Clinical Severity Scoring of Patients with Thrombotic Thrombocytopenic Purpura or the Hemolytic Uremic Syndrome

Score	Neurologic Symptoms	Renal Abnormalities	Platelet Count (per μL)	Hemoglobin Level (g/dL)
0	None	None	>100,000	>12
1	Confusion Lethargy	Serum creatinine = 1.5 to 2.4 mg/dL Proteinuria Hematuria	20,000–100,000	9–12
2	Seizure Coma Focal deficits	Serum creatinine ≥2.5 mg/dL Dialysis	<20,000	<9

long-term outcome. We also tracked the use of ancillary treatments, such as antiplatelet agents, corticosteroids, vincristine, splenectomy, and protein absorption columns, and conditions associated with the diagnosis, such as underlying malignancy, solid organ transplantation, and *Escherichia coli* H:0157 infection.

METHODS

Study Sample

The study sample included consecutive patients with TTP or hemolytic uremic syndrome of all ages who were referred to the therapeutic apheresis service of the Sacramento Medical Foundation Blood Center (a not-for-profit community blood center that serves 41 hospitals in a 17-county area of Northern California with an estimated 2.8 million residents) and the University of California Davis Medical Center from 1978 through 1998. The vast majority of patients referred for treatment were seen in the greater Sacramento area at 13 participating hospitals that include large city and smaller community hospitals. All patients were required to have microangiopathic hemolytic anemia, as characterized by schistocytes or red cell fragmentation on the peripheral blood smear, and thrombocytopenia (platelet count <150,000/μL), with no other identifiable cause for the anemia and thrombocytopenia (eg, disseminated intravascular coagulation, hypertensive crisis, or eclampsia). All patients had normal prothrombin and activated partial thromboplastin times.

Data Collection

A retrospective review of the medical records of the therapeutic apheresis service was conducted using standardized forms and an explicit abstraction process. Data unavailable from these records were obtained from hospital records, when available. We collected information on demographic characteristics (age, gender, race, date of initial treatment, and site of treatment), initial clinical presentation (presence of fever or neurologic abnormalities), laboratory values at the time of initial presentation (hemoglobin level, hematocrit, platelet count, and serum lactate dehydrogenase and creatinine levels), number of plasma exchanges required to achieve a complete response (see below), total number of plasma exchange treatments, total volume of plasma infused, selected medical conditions (underlying malignancy, solid organ transplants, mitomycin therapy, postpartum state, human immunodeficiency virus [HIV] infection, and *E. coli* H:0157 infection), and concurrent ancillary treatments for TTP or hemolytic uremic syndrome (corticosteroids, antiplatelet agents, vincristine, protein adsorption column, intravenous gamma globulins, hemodialysis, peritoneal dialysis, plasma infusion, and splenectomy). We were unable to measure red cell or platelet transfusions because of insufficient documentation in the available records.

Patients were assigned a Clinical Severity Score (14,15) based on four clinical and laboratory characteristics, if available, at the time of presentation (Table 1). The Severity Score incorporates neurologic, renal, and hematologic abnormalities and has a range of 0 to 8 points.

Treatment

Plasma exchange therapy was initiated within 24 hours of diagnosis at 1.5 times the predicted plasma volume for the initial procedure(s). All patients undergoing plasma exchange were treated in a relatively uniform fashion, with daily exchanges until there was stabilization of the platelet count above 100,000/μL associated with no new or progressive neurologic deficits and a declining serum lactate dehydrogenase level. When a response was achieved, a slow plasma exchange taper was initiated, usually involving every other day, three times weekly, or twice-weekly schedules before cessation of treatment. Before September 1993, plasma exchanges were performed using the Fenwal CS-3000 Blood Cell Separator (Fenwal, Deerfield, Illinois) or the Haemonetics model V50 (Haemonetics Corp., Braintree, Massachusetts) machines. After September

1993, all exchanges were performed using the Cobe Spectra (Cobe, Boulder, Colorado).

Outcome Variables

The primary study outcome was defined as death from TTP or the hemolytic uremic syndrome within 30 days of diagnosis and initiation of therapy. The secondary outcomes were response rates to plasma exchange, overall survival in patients who were followed after hospital discharge, and relapse rates. Mean follow-up was 2 years, with a range of 1 to 152 months. Long-term follow-up information after hospital discharge was collected through review of the appropriate office charts, follow-up questionnaires sent to the referring physician, and physician or patient interviews. Determination of cause of death was done through review of medical records and death certificates.

Response and Relapse Criteria

A complete response to plasma exchange was defined as a platelet count greater than 100,000/μL for two consecutive evaluations, declining serum lactate dehydrogenase levels (if initially elevated), and no further neurologic deficits or progression. A partial response was defined as stabilization of the platelet count below 100,000/μL with no further neurologic deficits or progression. We chose the 100,000/μL cutoff point because it was a more practical clinical value than the traditional 150,000/μL; to allow comparisons with previous reports using 150,000/μL as the response cutoff, we also evaluated our data using this level.

Four patients had platelet counts that were greater than 150,000/μL. These patients had actually been previously diagnosed (with platelet counts less than 150,000) and treated with a complete response but were later transferred to our centers for subsequent plasma exchange. The platelet counts available for abstraction were obtained from the day of transfer to one of our centers. Admission data were incomplete for these patients; thus, they were excluded from the primary analyses of 30-day mortality and relapse.

Patients who had progressive thrombocytopenia, worsening neurologic deficits, or clinical deterioration while undergoing plasma exchange therapy were deemed treatment failures. Relapse after a documented response was defined as the recurrence of any of the following: initial signs and symptoms, microangiopathic anemia, thrombocytopenia, or abrupt or slowly progressive deterioration in clinical status following cessation of plasma exchanges. Responding patients who did not return for follow-up visits after the initial hospitalization were censored from the determination of relapse. Neurologic impairment included headaches, mental status changes (including confusion, obtundation, and coma), acute sensory or motor deficits, and seizures. Patients who received fewer than four plasma exchanges or who did not receive plasma exchange as a principal treatment were not evaluable for response but were included in the mortality analysis.

Table 2. Patient Characteristics at the Time of Diagnosis

	Number (Percent) or Mean ± SD
Age (years)	49 ± 20
Female gender	83 (66)
Ethnicity	
White	89 (71)
Hispanic	17 (13)
African American	14 (11)
Asian	3 (2.5)
Other	3 (2)
Neurologic symptoms	83 (66%)
Fever	68 (54%)
Hemoglobin (g/dl)	8.9 ± 2.0
Platelet count (per μL)	44,000 ± 45,000
Serum lactate dehydrogenase (times upper limit of normal)	6.4 ± 9.0
Serum creatinine (mg/dL)	3.4 ± 2.6
Comorbid conditions	
Cancer	13 (10)
Solid organ transplant	6 (5)
HIV infection	6 (5)
Mitomycin-based therapy	6 (5)
E. coli 0157 infection	3 (2)
Sepsis	2 (2)
Hepatitis C	1 (<1)

HIV = human immunodeficiency virus.

Statistical Analysis

We determined the univariate and multivariate-adjusted associations of patient characteristics with 30-day mortality and with relapse rate. We also compared long-term survival among patients with and without serious underlying disorders (ie, cancer, solid organ transplantation, HIV infection, sepsis, hepatitis C, and *E. coli* H:0157 infection). Associations with 30-day mortality and relapse were assessed using the chi-square test and logistic regression models, using the backwards elimination method. Odds ratios (OR) and 95% confidence intervals (CI) are reported. Product-limit survival estimates were calculated using Kaplan-Meier methods. All analyses were performed using SAS (Cary, North Carolina). Statistical significance was set at $P < 0.05$. Continuous data are reported as means ± SD, unless otherwise noted.

RESULTS

Of the 126 patients, 95 (75%) had TTP, while the remainder had the hemolytic uremic syndrome. About two thirds of the patients were female, with an age range from 1.5 to 85 years (Table 2). Their ethnic distribution re-

flected the demographic characteristics of our region. About 30% of patients had an underlying serious medical disorder. The median platelet count was 29,000/μL, with a range from 7,000 to 121,000/μL; the median hemoglobin level was 9.1 g/dL with a range of 2.8 to 15.6 g/dL. The serum creatinine level was less than 1.5 mg/dL in 28% of patients, between 1.5 and 2.5 mg/dL in 26%, and greater than 2.5 mg/dL in 46%. The serum lactate dehydrogenase level was elevated above the upper limit of normal in all but 7 (6%) of the 116 patients in whom a lactate dehydrogenase level was available at the time of diagnosis. A Clinical Severity Score could be assigned to 119 patients. The mean score was 5 ± 5, with a median of 5 and a range of 2 to 8.

Plasma exchange was the principal treatment in 122 (97%) patients; the remaining 4 patients received either fresh frozen plasma infusion only (n = 2) or protein adsorption column therapy of their plasma only (n = 2). Ten patients received fewer than 4 plasma exchanges. Patients received a median of 9 plasma exchanges, with a range of 0 to 262 exchanges. The mean cumulative volume of fresh frozen plasma infused was 43 ± 77 L, with a median of 22 L. Corticosteroids were used in 22% of the patients, antiplatelet agents (aspirin or dipyridamole) in 16%, vincristine in 15%, and dialysis in 13%. Protein adsorption column therapy, intravenous immunoglobulins, splenectomy, and fresh frozen plasma infusion without exchange were each used in less than 5% of patients. One patient was also treated with ticlopidine.

Of the 126 patients, 2 had hospital charts that were unavailable for review. Thus 124 patients were considered evaluable for response to treatment. Using a cutoff value for the platelet count of 100,000/μL to define a response, 96 (77%) patients responded, including 70 (56%) complete responders and 26 (21%) partial responders. There were 16 (13%) treatment failures. Of the 14 (10%) patients who were not assessable for a response, 10 received fewer than 4 plasma exchanges. Using the 150,000/μL platelet cutoff, there were 56 (45%) complete responders and 40 (32%) partial responders.

Thirteen (10%) of the 124 patients died within the first 30 days following diagnosis, including 1 patient who died of an HIV-related infection. Of the 12 patients who died of TTP or the hemolytic uremic syndrome, 8 (67%) did not respond to plasma exchange, 3 (25%) did not receive at least 3 plasma exchanges (including 1 who refused treatment), and 1 had an initial complete response. Of the 86 patients with adequate follow-up data, 11 (13%) relapsed following an initial response. Time to relapse ranged from 3 weeks to 152 months. One of the 11 patients died of a myocardial infarction 13 years after the original diagnosis of TTP.

Associations with 30-day Mortality and Relapse

A higher Clinical Severity Score at the time of presentation was associated with a significantly greater risk of 30-day mortality (Table 3). Fever at initial presentation was associated with a lesser risk of relapse. These associations remained significant in multivariate models (Table 4). In addition, the greater the initial serum creatinine level, the lower the risk of relapse.

Effects of Underlying Medical Conditions

Patients with selected medical conditions that have been associated with TTP or the hemolytic uremic syndrome (Table 1) were not at an increased risk of 30-day mortality (OR = 0.7, 95% CI: 0.2 to 2.7, $P = 0.6$) or relapse (OR = 0.5, 95% CI: 0.1 to 2.4, $P = 0.4$). The estimated 2-year survival for the 72 patients without serious underlying comorbid conditions was about 80% (Figure). The overall estimated 2-year survival was about 60%, including patients with serious medical conditions.

Temporal Trends

The odds ratios for 30-day mortality (OR = 0.6, 95% CI: 0.2 to 2.6, $P = 0.4$) and relapse rate (OR = 0.9, 95% CI: 0.2 to 4.8, $P = 0.9$) were not significantly different in the pre-1988 era as compared with the post-1988 period.

DISCUSSION

We studied the effects of early, aggressive plasma exchange in the management of TTP and the hemolytic uremic syndrome. The overall response rate of 77% is remarkably similar to the 76% response to plasma exchange that was reported in a 1982 review (16). The observed 30-day mortality of 10% is comparable with the mortality rate of 9% reported by Bell et al (17), although in that series, all deaths occurred within 4 days of diagnosis and not all patients received plasma exchange therapy. In the plasma exchange arm of the Canadian Apheresis Study Group trial, the 4-week mortality rate was approximately 20% (6). Our cohort generally received greater volumes of infused fresh frozen plasma (a mean of 43 L) compared with the Canadian Apheresis Study Group trial (a mean of 21.5 L) (6).

The estimated 10-year survival of 50% was lower than expected. However, that estimate is based on a relatively small number of patients with follow-up beyond a few years. In addition, a substantial proportion of our patients were older than the median age of 41 years reported previously (18), and there were several patients who died from serious underlying comorbid conditions. However, our data confirm the improved survival in patients treated with plasma exchange without underlying comorbidities (5).

The Clinical Severity Score (14,15) is a potentially useful prognostic variable for short-term outcome. Other

Table 3. Univariate Associations between Patient Characteristics and 30-Day Mortality and Relapse*

Variable	Total Patients, N (%)	Patients Dying within 30 Days, N (%)	30-Day Mortality Odds Ratio (95% Confidence Interval)	*P* Value	Patients Relapsing, N (%)	Relapse Odds Ratio (95% Confidence Interval)	*P* Value
Clinical severity score							
3 or less	26 (22)	1 (1)	0.6 (0.06–5.0)	0.6	4 (5)	2.4 (0.8–11)	0.2
4 to 5	60 (50)	4 (5)	Reference		4 (5)	Reference	
6 or more	33 (28)	7 (8)	3.8 (1.0–14)	0.05	3 (3)	1.8 (0.4–9)	0.5
Per unit increase			2.5 (1.3 to 5.0)	0.007		1.6 (0.7–3)	0.2
Fever at presentation							
Absent	58 (46)	5 (3.4)	Reference		9 (7)	Reference	
Present	68 (54)	8 (6.4)	1.4 (0.4–5)	0.6	2 (2)	0.2 (0.04–0.9)	0.04
Age (years)							
<20	14	2 (5)	1.1 (0.2–7.6)	0.9	2 (5)	1.8 (0.2–15)	0.6
20–35	23	1 (2)	0.3 (0.03–3)	0.3	3 (6)	1.3 (0.2–9)	0.8
36–50	23	3 (6)	Reference		2 (5)	Reference	
51–65	41	3 (5)	0.5 (0.1–2.8)	0.5	4 (6)	0.9 (0.2–5)	0.9
>65	25	4 (8)	1.3 (0.3–6.4)	0.8	0		
Platelet count (per μL)							
<20,000	43	5 (4)	0.9 (0.2–5)	0.9	5 (6)	5.6 (0.6–50)	0.1
20,000–50,000	45	5 (8)	2.2 (0.5–9)	0.3	5 (6)	5 (4–45)	0.2
>50,000	38	3 (4)	Reference		3 (4)		
Hemoglobin (g/dL)							
<9.0	59	8 (7)	1.8 (0.6–6)	0.3	5 (4)	0.9 (0.3–2)	0.9
9.0–12.0	63	5 (4)	Reference		6 (5)		
<12.0	4	0			0		
Serum creatinine (mg/dL)							
<1.5	46	3 (4)	Reference		7 (9)	Reference	
1.5–2.5	29	3 (4)	1.7 (0.3–9)	0.6	2 (3)	0.4 (0.1–2)	0.3
>2.5	51	7 (7)	2.4 (0.6–10)	0.3	2 (2)	0.2 (0.05–1)	0.1

* There were no associations between gender, ethnicity, neurologic symptoms, or serum lactate dehydrogenase levels and either 30-day mortality or relapse.

factors, such as age, laboratory abnormalities, renal insufficiency, fever, and neurologic dysfunction, were not associated with 30-day mortality. Surprisingly, the absence of fever at presentation appears to be a risk factor for relapse, perhaps reflecting a suboptimal inflammatory response.

There are several important limitations that must be considered when interpreting the results of this study.

Table 4. Multivariate Associations (Logistic Regression Models) between Patient Characteristics and 30-Day Mortality and Relapse

Variable (Unit)	30-Day Mortality			Relapse		
	Odds Ratio	95% Confidence Interval	*P* Value	Odds Ratio	95% Confidence Interval	*P* Value
Clinical Severity Score (1 unit)	2.2	1.3–3.9	0.002	0.9	0.6–1.5	0.8
Fever at presentation	1.6	0.5–5.6	0.4	0.2	0.03–0.9	0.03
Age (10 years)	1.0	0.8–1.4	0.9	0.7	0.5–1.0	0.07
Platelets (20,000/μL)	0.9	0.7–1.2	0.9	0.7	0.4–1.1	0.1
Hemoglobin (1 g/dL)	0.9	0.7–1.2	0.6	0.9	0.7–1.3	0.9
Serum creatinine (1 mg/dL)	1.2	0.9–1.4	0.2	0.5	0.3–0.9	0.006
Lactate dehydrogenase (per multiple of twice the upper limit of normal)	1.0	0.8–1.1	0.9	0.9	0.6–1.1	0.2
Neurologic symptoms at presentation	3.5	0.9–23	0.08	1.7	0.5–8.2	0.4
Female gender	0.8	0.2–2.8	0.8	1.1	0.3–4.1	0.8

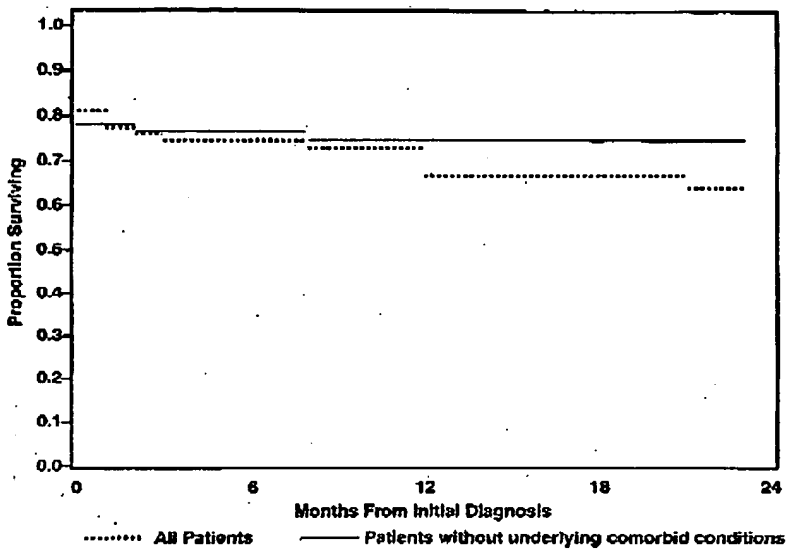

Figure. Kaplan-Meier survival curves for thrombotic thrombocytopenic purpura/hemolytic uremic syndrome patients. There were 86 patients at baseline and 23 patients for whom 2-year follow-up was available. The dotted line represents all patients, the solid line represents patients without serious underlying comorbid conditions.

First, data were collected by review of medical and apheresis treatment records, which may bias the assessments of the response and relapse rates. Second, this analysis contains patients seen during a 20-year time span, during which ancillary therapies and health care providers changed, and different apheresis machines were used. The influence of ancillary treatments was not analyzed because of the small numbers of patients who received those treatments. Third, follow-up and mortality data were unavailable for a substantial number of patients. Some of the follow-up data were obtained from physician and patient interviews, and thus subject to recall bias.

Early, aggressive plasma exchange appears to be safe, efficacious, and feasible in the treatment of patients with TTP and the hemolytic uremic syndrome, with good short- and long-term outcome. Subsequent studies might address the relative importance of plasma exchange frequency and intensity, and evaluate the effects of ancillary treatments such as cryosupernatant frozen plasma and vincristine in patients at high risk, as defined by the Clinical Severity Score.

REFERENCES

1. Moschowitz E. Acute febrile pleiochromic anemia with hyaline thrombosis of terminal arterioles and capillaries: an undescribed disease. *Arch Intern Med.* 1925;36:89–93.
2. Ruggenenti P, Remuzzi G. The pathophysiology and management of thrombotic thrombocytopenic purpura. *Eur J Hematol.* 1996;56: 191–207.
3. Gillis S. The thrombocytopenic purpuras: recognition and management. *Drugs.* 1996;51:942–953.
4. Gasser C, Gautier E, Steck A, et al. Haemolytisch-uramische syndrome: bilaterale nierenrindennekrosen bei akuten erworbenen hamolytischen anamien. *Schweiz Med Wochenschr.* 1955;85:905–909.
5. Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *NEJM.* 1982;307:1432–1435.
6. Furlan M, Robles R, Galbusera M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. *NEJM.* 1998;339:1578–1584.
7. Tsai HM, Lian E. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *NEJM.* 1998;339:1585–1594.
8. Tarantolo SR, Landmark JD, Iwen PC, et al. Bartonella-like erythrocyte inclusions in thrombotic thrombocytopenic purpura. *Lancet.* 1997;350:1602.
9. Tarantolo SR, Landmark JD, Hinrichs SH, et al. Bartonella-like erythrocyte inclusions associated with post-transplant thrombotic microangiopathy. *Blood.* 1997;90(suppl):1109.
10. Amorosi EL, Ultman JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of literature. *Medicine.* 1966;45:139–159.
11. Kwaan H, Soff G. Management of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Semin Hematol.* 1997;34: 159–166.
12. Rock G, Shumak K, Buskard N, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *NEJM.* 1991;325:393–397.
13. Ruggenenti P, Remuzzi G. Thrombotic thrombocytopenic purpura and related disorders. *Hematol Oncol Clin North Am.* 1990;4:219–241.
14. Rose M, Eldor A. High incidence of relapses in thrombotic thrombocytopenic purpura: clinical study of 38 patients *Am J Med.* 1987; 83:437.

15. Welborn JL, Emrick P, Acevedo M. Rapid improvement of thrombotic thrombocytopenic purpura with vincristine and plasmapheresis. *Am J Hematol.* 1990;35:18–21.
16. Bukowski RM. Thrombotic thrombocytopenic purpura: a review. In: Spaet TH, ed. *Progress in Hemostasis and Thrombosis.* New York: Grune and Stratton; 1982:287–337.
17. Bell W, Braine HG, Ness P, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *NEJM.* 1991;325:398–403.
18. Elkins SL, Wilson PP, Files JC, Morrison FS. Thrombotic thrombocytopenic purpura: evolution across 15 years. *J Clin Apheresis.* 1996; 11:173–175.